REMARKS

Applicants have received and reviewed an Office Action dated September 11, 2006. Applicants thank the Examiner for acknowledging election of Group I in the response filed June 16, 2006.

By way of response to the present Office Action, Applicants note that the specification has been amended to properly recite priority information. Claims 41, 43, 48, 49, 50, 51, 54–56, 60–63, 67, 70, 75–76, 79–81 and 86 are currently pending. Applicants have canceled claims 42, 44–47, 52–53, 58–59, 64–66, 68–69, 71–72, 77–78 and 82–85 without prejudice. Claims 41, 43, 50, 51, 54, 55, 57, 60, 61, 63, 67, 70, 75, 76, 79–81 and 86 are currently amended. Claims 1–40 were previously canceled, and claims 73–74 were previously withdrawn in response to a restriction requirement. No new matter is presented. Applicants submit that the pending claims are supported by the specification.

For the reasons given below, Applicant submits that the amended and newly presented claims are in condition for allowance and notification to that effect is earnestly solicited.

Priority

Applicants thank the Examiner for bringing the missing priority information to Applicants' attention. The specification is amended herewith to properly claim priority to PCT/EP91/00743.

Objections to the Claims

The Examiner objected to claims 50–62 and 67–69 for informalities (i.e. certain typographical errors). Claims 50 and 67 have been amended to correct the typographical errors. Withdrawal of the objection is requested.

Rejections under 35 U.S.C. § 112, first paragraph

(1) The Examiner rejected claims 41–72 and 75–86 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner contends that because the claims recite nucleic acids comprising sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of any non-viral organism, the

genus includes millions of highly diverse organisms with substantially different nucleotide sequences. Applicants traverse the rejection.

The written description requirement is satisfied when Applicants' specification conveys with reasonable clarity to those skilled in the art, that as of the filing date sought, he or she was in possession of the invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). A written description of an invention involving a chemical genus requires a precise definition, such as by structure, formula, etc. of the claimed subject matter sufficient to distinguish it from other materials. Univ. of California v. Eli Lilly and Co., 43 USPQ2d 1398. 1405 (Fed. Cir. 1997) (emphasis added). Since one skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass, such a formula is normally an adequate description of the claimed invention. Id. at 1406 (emphasis added).

Without acquiescing in the rejection and solely in the interest of expediting allowance of these claims, Applicants note that the claims have been amended to recite nucleic acids comprising sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism. Support for this amendment can be found throughout the specification (*see, e.g.*, page 6, ll. 11–23). Applicants submit that detection of the prokaryotic microorganism using these nucleic acids depends on specific hybridization of the nucleic acids with a target sequence. The specification clearly indicates that probes that specifically hybridize are those that do not cross-react with nucleic acids from other organisms (*see, e.g.*, page 1, ll. 22–24). The claims, as amended, describe the nucleic acids according to the overall length (for example, 15 to 100 contiguous nucleotides) and by a specific source (i.e. a prokaryotic microorganism). Applicants submit that such description is sufficient to meet the requirements of § 112, first paragraph, and respectfully request withdrawal of the rejection.

Claim 81 was rejected under 35 U.S.C. § 112, first paragraph, as failing to meet the written description requirement. Specifically, the Examiner indicates that the specification provides no support for the concept of immobilizing primers to a solid support. Applicants respectfully disagree. The specification notes that the oligonucleotides of the invention can be either probes used to detect amplified fragments, or primers for PCR. The specification further notes that PCR-assisted hybridization can be used in the methods of the invention (*see, e.g.*, page 41, ll. 6–14). The oligonucleotides (i.e. probes or primers) can be dot-spotted on a known

location (*see, e.g.*, page 42, ll. 6–8), or fixed to a solid support (*see, e.g.*, page 45, ll. 11–12). Therefore, the specification provides adequate written description for the recitation of immobilizing primers to a support. Applicants respectfully request withdrawal of the rejection.

(2) The Examiner rejected claims 41–72 and 75–86 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the Examiner contends that the specification does not enable a person of skill in the art to make and use the invention commensurate to the scope of the claims. Applicants respectfully traverse the rejection.

The test of enablement is whether a person skilled in the art to which the invention pertains could make or use the invention from the disclosure in the specification without undue experimentation. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.3d 1367, 1384 (Fed. Cir. 1986). The fact that complex experimentation may be required does not necessarily make the experimentation undue. In re Wands, 858 F.2d 731 (Fed. Cir. 1988). Where the level of skill in the art is very high, and all of the methods used to practice the invention are well known, experimentation is typically not undue. Id. at 736. The burden of establishing a lack of enablement is on the Examiner. Genentech v. Wellcome Foundation, 29 F.3d 1555, 1563 (Fed. Cir. 1994).

Without acquiescing in the rejection and solely in the interest of expediting allowance of these claims, Applicants note that the claims have been amended to recite nucleic acids consisting of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism. Support for this amendment can be found throughout the specification (*see, e.g.*, page 6, ll. 11–23). Applicants submit that detection of the prokaryotic microorganism using these nucleic acids depends on specific hybridization of the nucleic acids with a target sequence. The specification clearly indicates that probes that specifically hybridize are those that do not cross-react with nucleic acids from other organisms (*see, e.g.*, page 1, ll. 22–24). The claims, as amended, describe the nucleic acids according to the overall length (for example, 15 to 100 contiguous nucleotides) and by a specific source (i.e. a prokaryotic microorganism). Applicants submit that such description is sufficient to meet the enablement requirement, and respectfully request withdrawal of the rejection.

Rejections under § 112, second paragraph

The Examiner rejected claims 41–72 and 75–86 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants traverse the rejection.

The Examiner contends that the term "RNA form" in claims 41–72 and 75–86 is indefinite, because it is not clearly defined in the specification and does not have a recognized meaning in the art. Applicants respectfully disagree with this contention. The specification indicates that the probes of the invention that hybridize with the sequences located in the spacer region between large and small (or large and 5S) rRNA subunits are formed of DNA or RNA fragments, or cloned fragments or synthetic oligonucleotides (*see, e.g.*, page 13, ll. 16–23). Therefore, the term "RNA form" refers the an RNA molecule that is similar to the claimed nucleic acid molecules, except that T has been replaced with U, i.e. the "RNA form" of the claimed nucleic acid. As the term is properly defined in the specification, Applicants respectfully request withdrawal of the rejection.

The Examiner contends that the term "able to hybridize specifically to a target" is indefinite. Applicants disagree, and submit that the term is adequately defined in the specification. The specification notes that the probes of the invention should be highly specific, i.e. they should not cross-react with nucleic acids from other organisms. In the context of the present claims, the term "hybridize specifically" implies that the probes or primers of the invention hybridize only to target sequences from the prokaryotic microorganism being detected using the probe in the methods of the invention. For example, in a method for detecting *Neisseria gonorrhea*, the probe hybridizes with DNA and RNA of *N. gonorrhea*, but not to DNA or RNA from other microorganisms (*see* page 26, l. 32 to page 27, l. 4). As the term is clearly defined, Applicants respectfully request withdrawal of the rejection.

The Examiner rejected claims 50–62 as indefinite, because several terms in these claims lacked antecedent basis. Applicants note that the claims have been amended to provide proper antecedent basis, and respectfully request withdrawal of the rejection.

The Examiner rejected claims 41–47 for failing to recite a final process step which clearly relates back to the preamble. Specifically, the Examiner notes that the claims recite methods for detecting a plurality of microorganisms but recite "at least one microorganism" in

the final process step. As an initial matter, Applicants note that as claims 41–47 are directed to the isolated nucleic acids and are not method claims, Applicants do not understand the nature of the rejection. However, with respect to the pending method claims, Applicants note that none of the pending claims recite "at least one microorganism." Therefore, Applicants request withdrawal of the rejection.

The Examiner rejected claims 63–66 as indefinite because the claims recite only a step of "using" a target, but do not recite how the target is used to detect an organism. Without acquiescing in the rejection, Applicants note that claim 63 has been amended to recite a step of using a target to detect an organism by hybridization. The process of hybridization of the probes is described in the specification, and furthermore, the term is understood as a method of detection by those of skill in the art. Therefore, the claims are definite and Applicants request withdrawal of the rejection.

The Examiner rejected claims 67–72 as indefinite because the claims recite a comparison step, but do not indicate how nucleotide sequences are compared to other unspecified nucleotide sequences. Without acquiescing in the rejection, Applicants note that claim 67 has been amended to recite a comparison step where the nucleotide sequences are compared to known nucleotide sequences in a database. Applicants submit the claims are now definite and respectfully request withdrawal of the rejection.

The Examiner rejected claims 79 and 84 as indefinite for reciting a method step of "labeling the amplified product" when the claims are directed to kits rather than methods. The Examiner also rejected claims 81 and 86 as indefinite for reciting a method step of "immobilizing the primer/probe" when the claims are directed to kits rather than methods. Applicants note that claim 79 has been amended to recite an agent for labeling the amplified products as a component of a kit. Claim 84 is canceled without prejudice as redundant in view of amendments to other claims. Similarly, claims 81 and 86 are amended to recite a solid support with a primer/probe immobilized on the support as a kit component. Withdrawal of the rejection is requested.

Double Patenting

The Examiner rejected claims 41–43, 46–63, 65–67, 69–70, 72, 75–76, 78–81 and 83–86 under the judicially-created doctrine of obviousness-type double patenting as unpatentable over

claims 1–3 of US 5,535,638, claims 1–46 of US 5,945,282 and claims 1–52 of US 6,277,577. Applicants respectfully traverse this rejection.

The present claims, as amended, are directed to isolated nucleic acid molecules consisting of a sequence within the spacer region between the large sub-unit and the small sub-unit (or the large subunit and the 5S subunit) of rRNA genes of a prokaryotic microorganism. This recitation is not inclusive of the probes, or methods, claimed in the patents above, which are probes from a transcribed spacer region between the 16S and 23S rRNA genes, or methods using such probes. Given the differences in the spacer region sequences identified in the present claims and in the claims of the patents above, Applicants submit that the present claims are patently distinct from those in the patents above, and respectfully request withdrawal of the double patenting rejection.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 41–50, 52, 53 and 63–65 under 35 U.S.C. § 102(e) as being anticipated by Kohne (US 5,928,684). Applicants respectfully traverse this rejection.

For anticipation, the cited reference must teach every limitation of the claim, either expressly or inherently. Verdegaal Bros. v. Union Oil Co. of Calif., 814 F.2d 628, 631 (Fed. Cir. 1987). If a claim covers several structures, then the claim is anticipated if any of the structures within the scope of the claims are known in the prior art. Brown v. 3M, Inc., 265 F.3d 1349, 1351 (Fed. Cir. 2001). If a person of skill in the art can "at once envisage" the claimed compound from the structural formula of the genus, the compound is anticipated. In re Petering, 301 F.2d 676 (CCPA 1962); see also MPEP § 2131.02 (8th ed. 2001, rev. 2006).

The present claims are directed to isolated nucleic acids consisting of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism. Furthermore, the claims as amended expressly indicate that the nucleic acids do not contain sequences of tRNA genes. Use of the "consisting of" language in the present claims means that the claims do not encompass precursor rRNA sequences or tRNA genes. Applicants submit that the claimed nucleic acid molecules and probes are not disclosed in the Kohne reference.

The Kohne reference discloses methods for detecting microorganisms by hybridizing probes to a sample nucleic acid that indicates the presence of the microorganisms. The probes are tRNA sequences specific to particular microorganisms, and also consist of precursor rRNA

sequences. The Kohne reference does not disclose methods using probes that consist of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism, nor does the reference disclose probes that do not have tRNA genes or precursor rRNA sequences. Because all the elements of the present claims are not disclosed in the Kohne reference, the claims are not anticipated. Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 41, 43–49 and 70–72 under 35 U.S.C. § 102(b) as being anticipated by White (in *PCR Protocols: A Guide to Methods and Applications*, pp. 315–22 (Acad. Press. NY 1990)). Applicants traverse this rejection.

The present claims, as amended, are directed to methods for detecting prokaryotic microorganisms, using isolated nucleic acids consisting of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism. Furthermore, the present claims recite methods using probes that consist of nucleic acids or oligonucleotides do not include tRNA genes.

The White reference discloses methods for the specific detection of eukaryotic microorganisms, using primers complementary to conserved sequences in the large and small rRNA subunits of eukaryotic species. The White reference does not disclose the use of tRNA-free probes in the described methods. As all the elements of the present claims are not disclosed in the White reference, the claims are not anticipated. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103

(1) The Examiner rejected claim 56 under 35 U.S.C. § 103(a) as obvious over Kohne (discussed above) and Saiki (*PNAS.* **86**: 6230–34 (1989)). Applicants traverse this rejection.

To make a *prima facie* case of obviousness, three criteria must be met. There must be (i) a teaching or suggestion in the cited references to modify the references or combine the teachings of the references; (ii) a reasonable expectation of success, and (iii) a teaching or suggestion of all the claim limitations on a cited reference, or combination of reference. See In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). The Examiner has the burden to establish a *prima facie* case of obviousness. The mere fact that references can be combined does not render a claimed

invention obvious unless the cited art suggests the desirability of the combination. In re Mills, 916 F.2d 680 (Fed. Cir. 1990). Furthermore, the Examiner cannot rely on the skill in the art to provide the suggestion to combine references, unless such a suggestion appears in the cited references. Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308 (Fed. Cir. 1999). If an independent claim is nonobvious, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071 (Fed. Cir. 1988).

The present claims are directed to isolated nucleic acids consisting of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism. Furthermore, the claims as amended expressly indicate that the nucleic acids do not contain sequences of tRNA genes. Use of the "consisting of" language in the present claims means that the claims do not encompass precursor rRNA sequences or tRNA genes. Applicants submit that such nucleic acid molecules and probes are not taught or suggested in the Kohne reference, either alone or in combination with the Saiki reference.

The arguments and remarks provided above (with respect to anticipation) are also fully relevant here and are incorporated by reference to avoid repetition. As discussed above, the Kohne reference does not disclose methods using probes that consist of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism, nor does the reference disclose probes that do not have tRNA genes or precursor rRNA sequences. The Saiki reference, when combined with the Kohne reference, does not provide the teaching missing from the Kohne reference. The Saiki reference teaches only that nucleic acids can be detected using "reverse dot blot" methods, but does not teach or suggest employing a nucleic acid probe as recited in the present claims.

Because all the elements of the present claims are not disclosed in the combination of the Kohne and Saiki references, a *prima facie* case of obviousness has not been made. Therefore, Applicants request withdrawal of the rejection.

(2) The Examiner rejected claims 51, and 57–59 under 35 U.S.C. § 103(a) are obvious over Kohne in view of White. Applicants respectfully traverse the rejection.

The arguments and remarks provided above are also fully relevant here and are incorporated by reference to avoid repetition. As indicated above, the Kohne reference does not disclose methods using probes that consist of sequences of a spacer region between the large and

small (or large and 5S) rRNA subunits of a prokaryotic microorganism, nor does the reference disclose probes that do not have tRNA genes or precursor rRNA sequences. The combination of Kohne and White references does not cure this deficiency. As discussed above, the White reference discloses methods for the specific detection of eukaryotic microorganisms. The White reference does not disclose the use of tRNA-free probes in the described methods.

Because all the elements of the present claims are not disclosed in the combination of the Kohne and White references, a *prima facie* case of obviousness has not been made. Therefore, Applicants request withdrawal of the rejection.

(3) The Examiner rejected claims 54, 55 and 60–62 under 35 U.S.C. § 103(a) as obvious over Kohne in view of White and further in view of Saiki. Applicants respectfully traverse the rejection.

The arguments and remarks provided above are also fully relevant here and are incorporated by reference to avoid repetition. To summarize briefly, neither the combination of Kohne and White references, nor the combination of Kohne and Saiki references provided a teaching or suggestion of probes, or methods using probes, that consist of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism, or probes that do not have tRNA genes or precursor rRNA sequences. Therefore, the combination of the Kohne, White and Saiki references fails to teach or suggests all the elements of the present claims. Therefore, no case of prima facie obviousness has been made, and Applicants respectfully request withdrawal of the rejection.

(4) The Examiner rejected claims 75–78, 82 and 83 under 35 U.S.C. § 103(a) as obvious over Kohne in view of the Stratagene Catalog (1998). Applicants traverse this rejection.

The arguments and remarks provided above are also fully relevant here and are incorporated by reference to avoid repetition. As discussed above, the Kohne reference does not disclose probes, or methods using probes, that consist of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism, nor does the reference disclose probes that do not have tRNA genes or precursor rRNA sequences. This deficiency of Kohne is not cured by combination with the Stratagene reference.

The Stratagene Catalog provides a general disclosure of kits for nucleic acid manipulations and hybridization methods. However, the Stratagene catalog fails to teach or suggest kits that include probes that consist of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism. Furthermore, the reference does not disclose probes that do not have tRNA genes or precursor rRNA sequences.

Therefore, as the combination of Kohne and the Stratagene catalog does not teach all the limitations of the present claims, the claims are not obvious. Withdrawal of the rejection is requested.

(5) The Examiner rejected claims 79, 80, 81 and 86 under 35 U.S.C. § 103(a) as obvious over Kohne in view of Saiki and further in view of the Stratagene Catalog. Applicants traverse this rejection.

The arguments and remarks provided above are also fully relevant here and are incorporated by reference to avoid repetition. To summarize briefly, neither the combination of Kohne and Saiki references, nor the combination of the Kohne reference and the Stratagene Catalog provided a teaching or suggestion of probes, or methods using probes, that consist of sequences of a spacer region between the large and small (or large and 5S) rRNA subunits of a prokaryotic microorganism, or probes that do not have tRNA genes or precursor rRNA sequences. Therefore, the combination of the Kohne and Saiki references with the Stratagene Catalog fails to teach or suggest all the elements of the present claims.

No *prima facie* case of obviousness has been made in view of the fact that all the elements of the claims are not taught in the combination asserted by the Examiner. Therefore, Applicants request withdrawal of the rejection.

SUMMARY

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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